# Simplification of Successful Antiretroviral Therapy with Nucleoside Analogues: Studies and Clinical Practice

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# Rationale for simplification of PI-HAART with NRTI or NNRTI

**Supporting adherence**

- less pill burden
- no dietary restriction
- reduction in adverse events (GIT)

**Preventing or reversing metabolic complications**

- hyperlipidemia
- fat accumulation

**Avoiding CYP interactions (NRTI)**

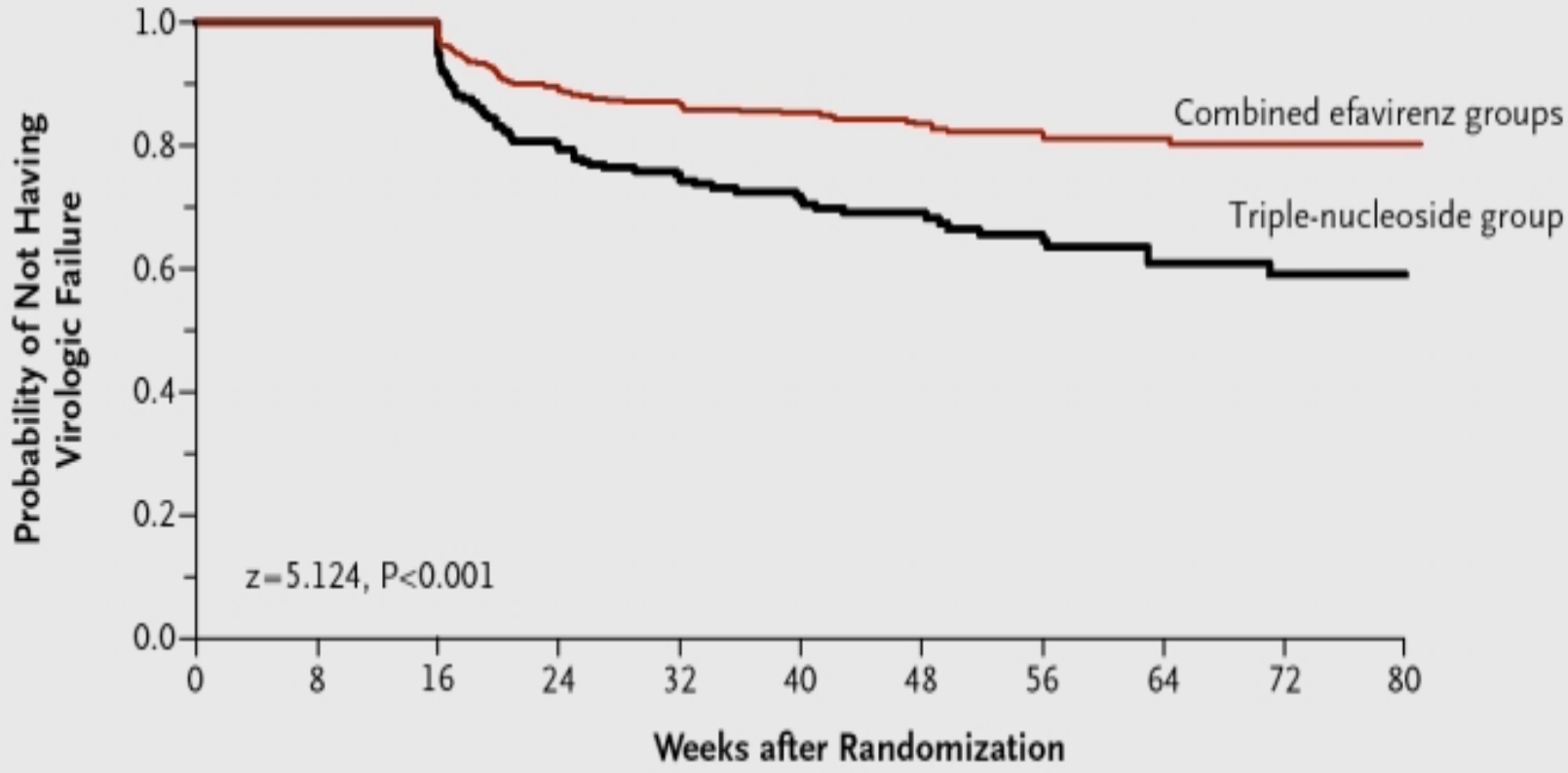
**Equal efficacy and durability as PI continuation ?**

- virological, also in lymphoid tissue
- immunological

**Other / new toxicity ?**

- mitochondrial toxicity, lipoatrophy (NRTI)
- rash (ABC, NNRTI)
- CNS (EFV)
- liver (NNRTI)

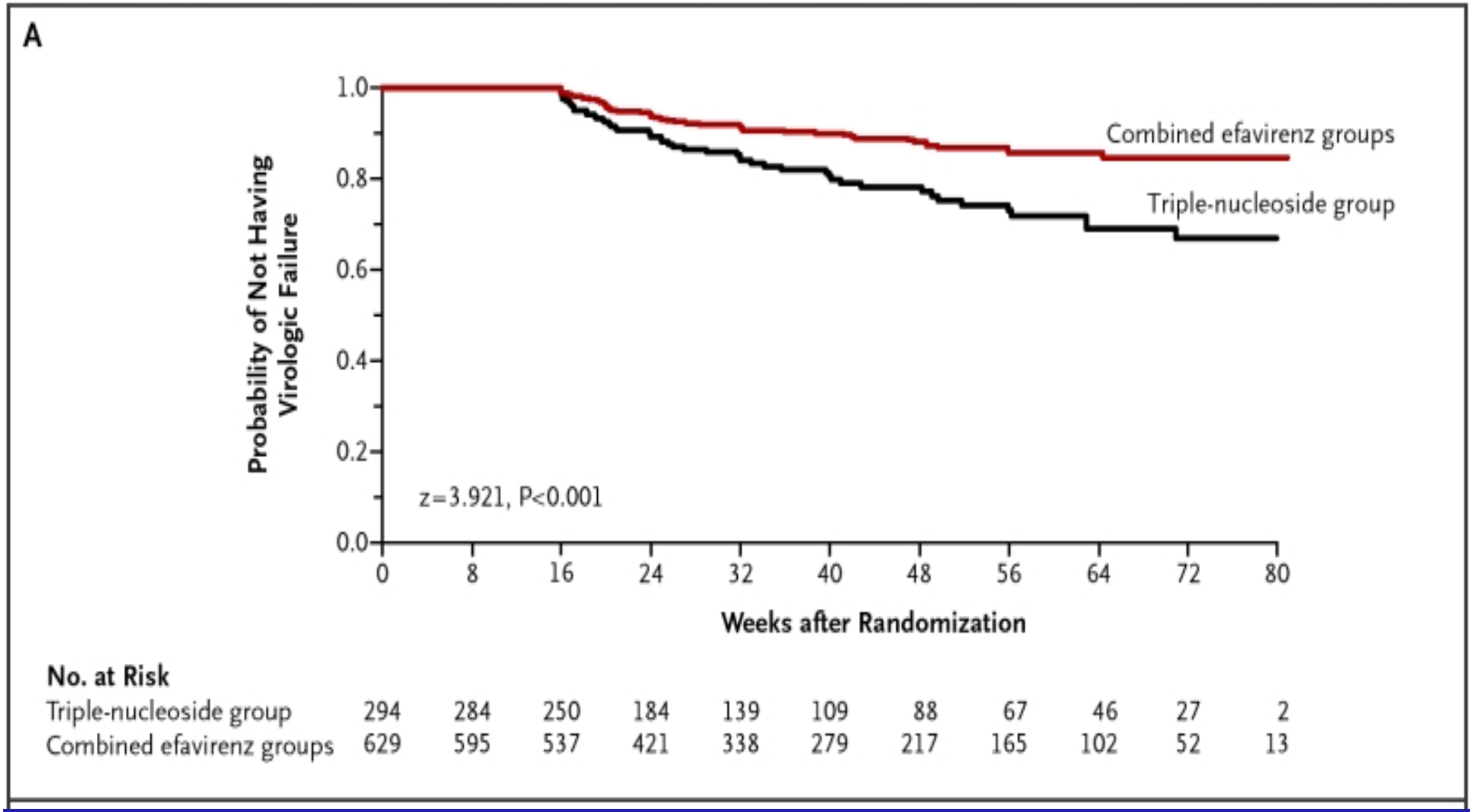
# ACTG5095: randomized, double-blind study of 3 regimens for the initial treatment of HIV: zidovudine–lamivudine–abacavir, zidovudine–lamivudine plus efavirenz, and zidovudine–lamivudine–abacavir plus efavirenz




| No. at Risk | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Triple-nucleoside group | 382 | 329 | 282 | 185 | 139 | 109 | 88 | 67 | 46 | 27 | 2 |
| Combined efavirenz groups | 765 | 653 | 576 | 421 | 338 | 279 | 217 | 165 | 102 | 52 | 13 |

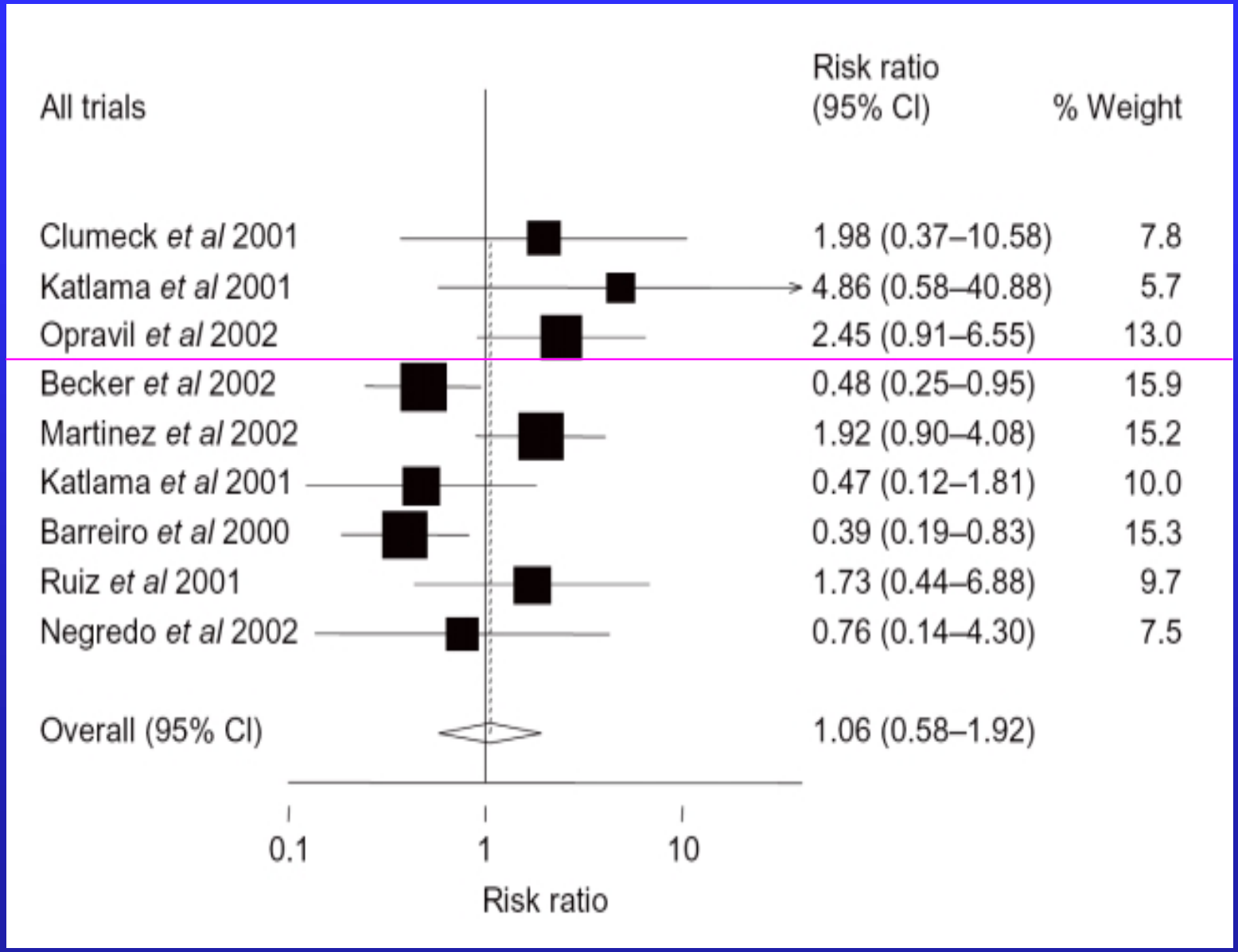
Gulick et al., NEJM 2004;350:1850

# ACTG5095: Virologic failure in pts with at least once HIV RNA <200 c./ml – Less durable effect of triple NRTI




Gulick et al., NEJM 2004;350:1850

# Meta-analysis of 9 randomized controlled trials of simplified versus continued PI-based HAART: virologic failure

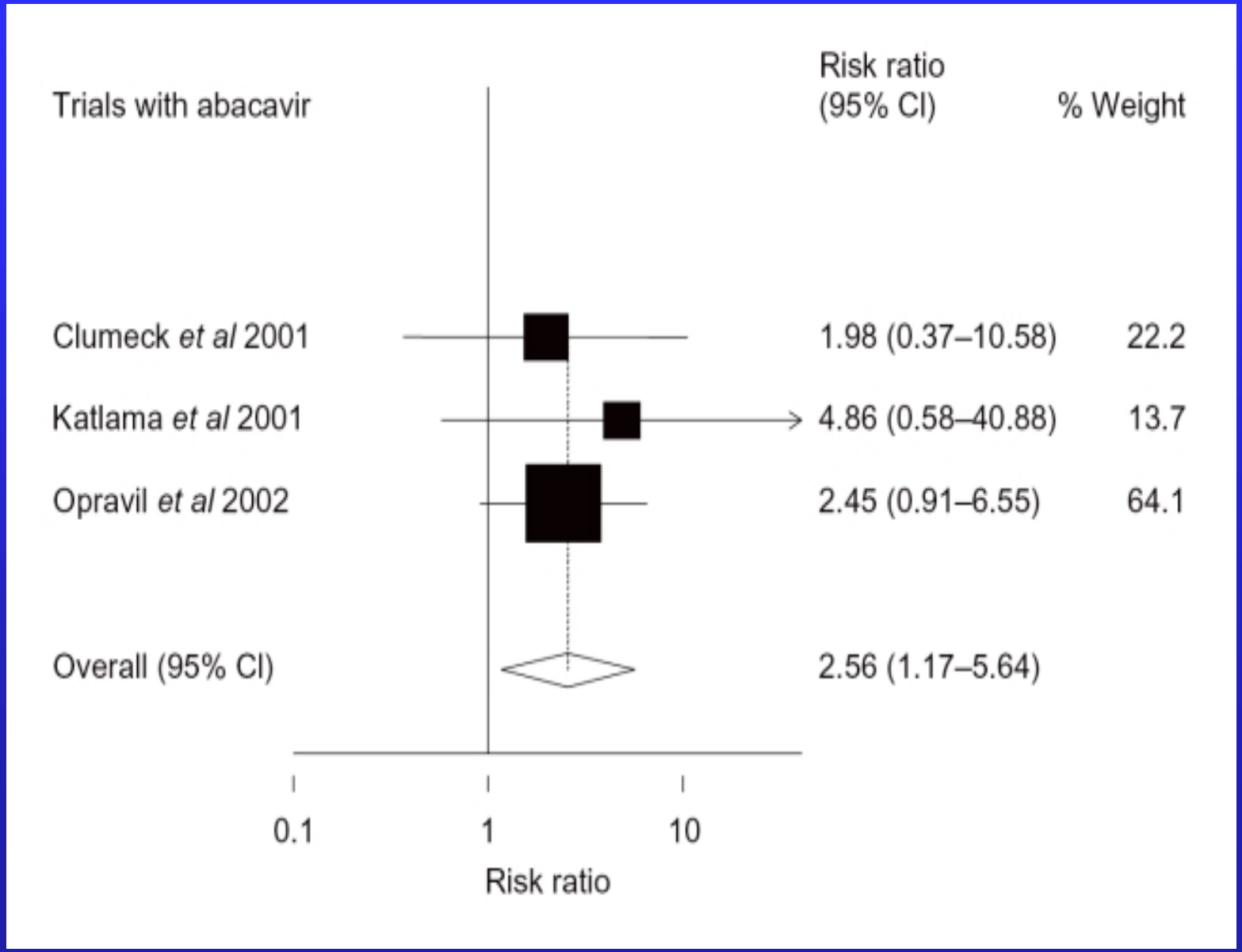



ABC / Trizivir

NNRTI

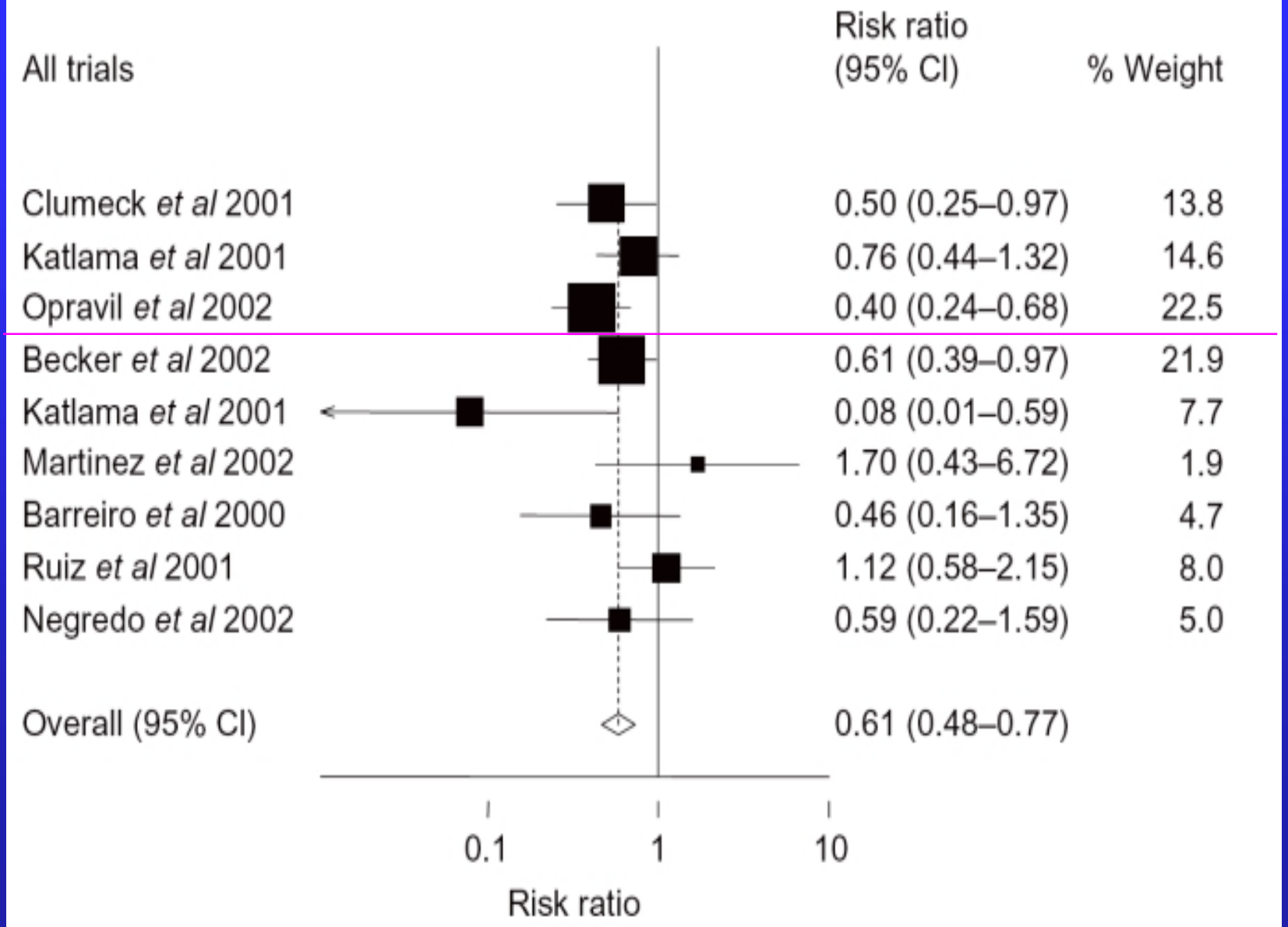
Bucher et al., AIDS 2003;17:2451-2459

# Meta-analysis of 3 randomized controlled trials of simplification to ABC / Trizivir: virologic failure




Bucher et al., AIDS 2003;17:2451-2459

# Discontinuation of therapy (secondary endpoint)




Bucher et al., AIDS 2003;17:2451-2459

**Studies in which some patients received sub-optimal regimens prior to HAART**

# NEV/EFA/ABA Trial

## Virological failure (VF) by previous therapy

| N patients | NEV N = 155 | EFA N = 156 | ABA N = 149 |
|---|---|---|---|
| Suboptimal Rx+HAART (n=237) | 5 | 4 | 14 |
| Only HAART (n=223) | 3 | 1 | 2 |
| Total VF | 8 | 5 | 16 |

Martinez et al., NEJM 2003;349:1036-46

## SMT Study Design

**Initial mono/dual NRTI (46%)**

**PI-containing HAART**

**HIV-1 RNA undetectable ≥ 6 months induced by PI-containing HAART**

**Randomize**

**Continue**

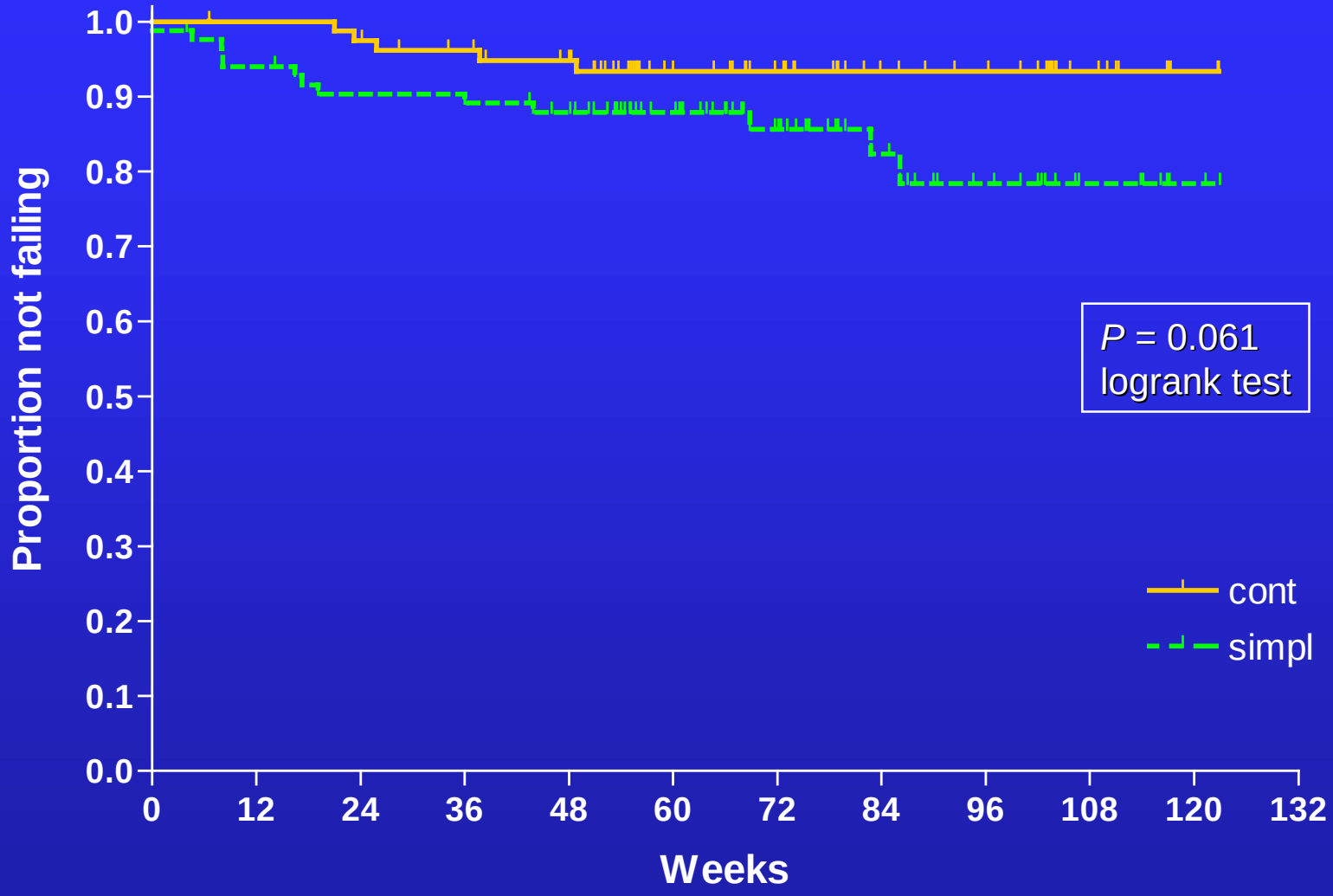
**Switch to ABC + COM (Trizivir >Mar 2000)**

**At screening:**

- **negative for 215 ZDV resistance mutation (PBMC DNA)**
- **<50 HIV-1 RNA copies/ml**

Opravil et al., JID 2002;185:1251-60

# SMT: Time to virologic failure (ITT analysis)




| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| N (cont.): | 79 | 79 | 77 | 73 | 68 | 45 | 34 | 25 | 22 | 10 | 3 |
| N (simpl.): | 84 | 80 | 75 | 74 | 71 | 53 | 38 | 24 | 16 | 8 | 3 |

Opravil et al., JID 2002;185:1251-60

# Treatment failure vs. virologic failure

**Change of treatment due to AE or preference**

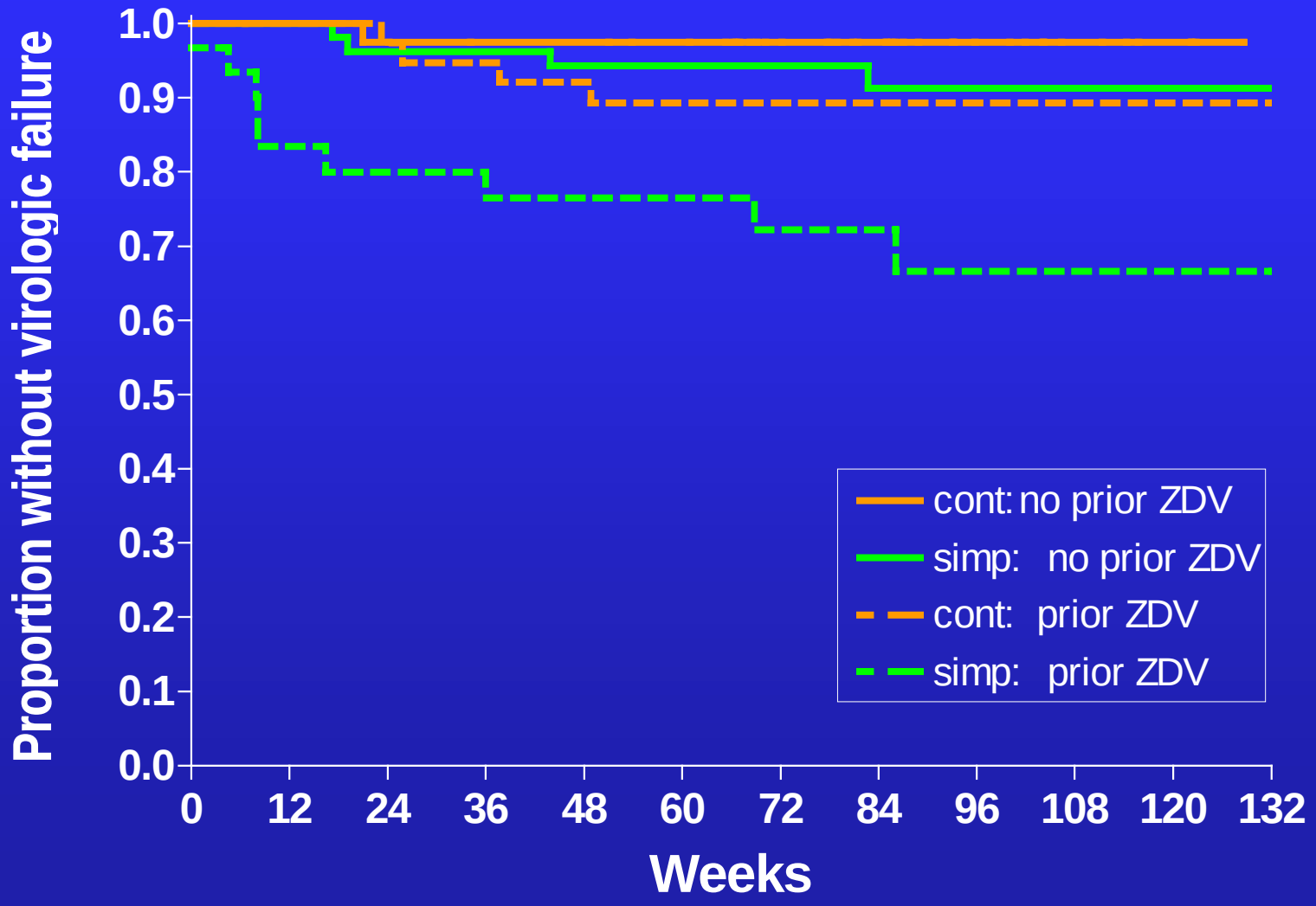
- **Today many options**
- **May even be desirable if it improves adherence**

**Virologic failure**

- **More severe because resistance possible: decreases future treatment options**

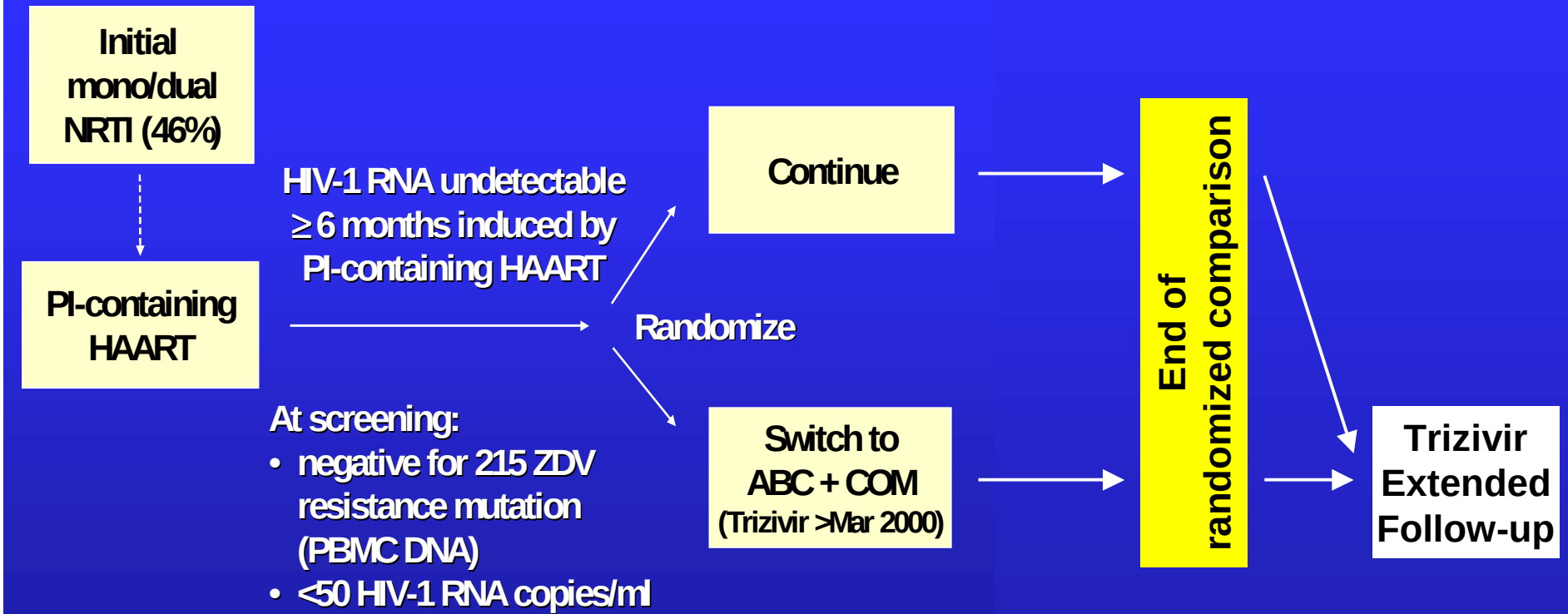
# SMT: Time to virologic failure (ITT analysis)

## Pre-treatment with ZDV before HAART predicts virologic failure

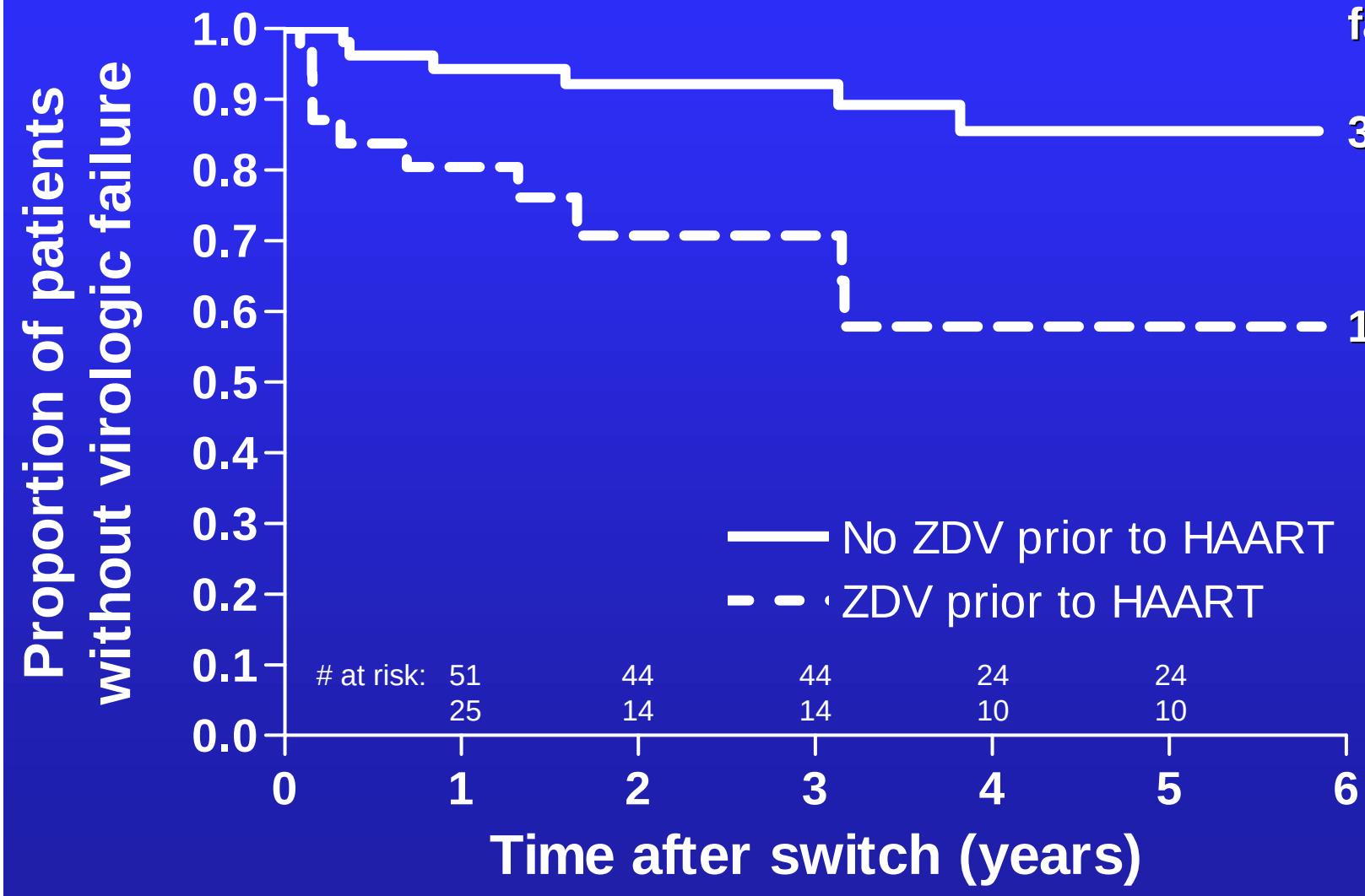



Opravil et al., JID 2002;185:1251-60

# SMT: original study + extended follow-up



# SMT study: long-term efficacy




**incidence of virologic failure:**

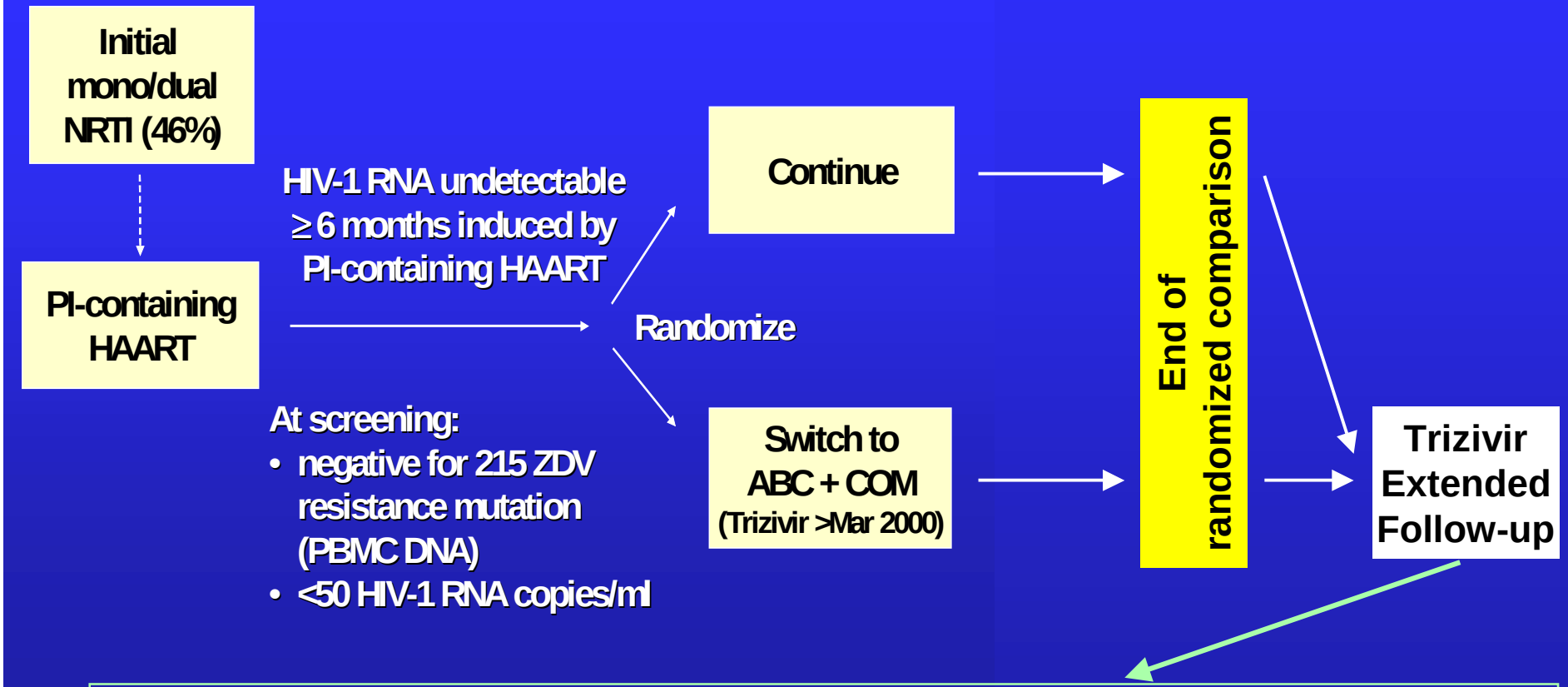
**3.4/100 PY (N = 53)**

**13.5/100 PY (N = 31)**

**(*P* = 0.008)**

Opravil et al., AIDS 2004 in print

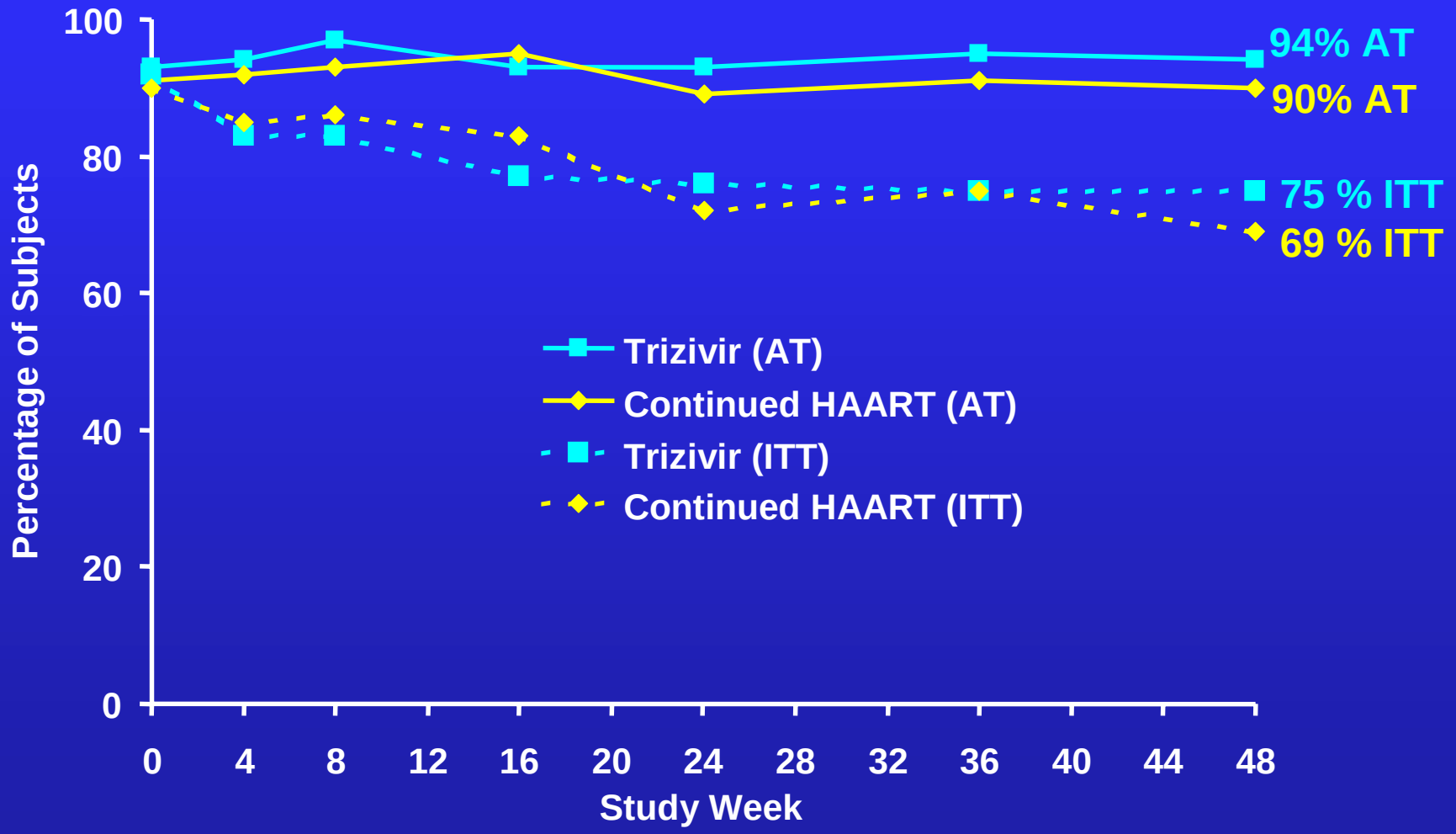
# SMT design: original study + extended follow-up




Virologic failure among all 81 patients without prior ZDV mono/dual therapy who switched from PI-regimens to Trizivir:
2.45/100 PY (95% Poisson CI: 0.90 – 5.33/100 PY)

**Subjects with a history of mainly HAART from initiation of therapy**

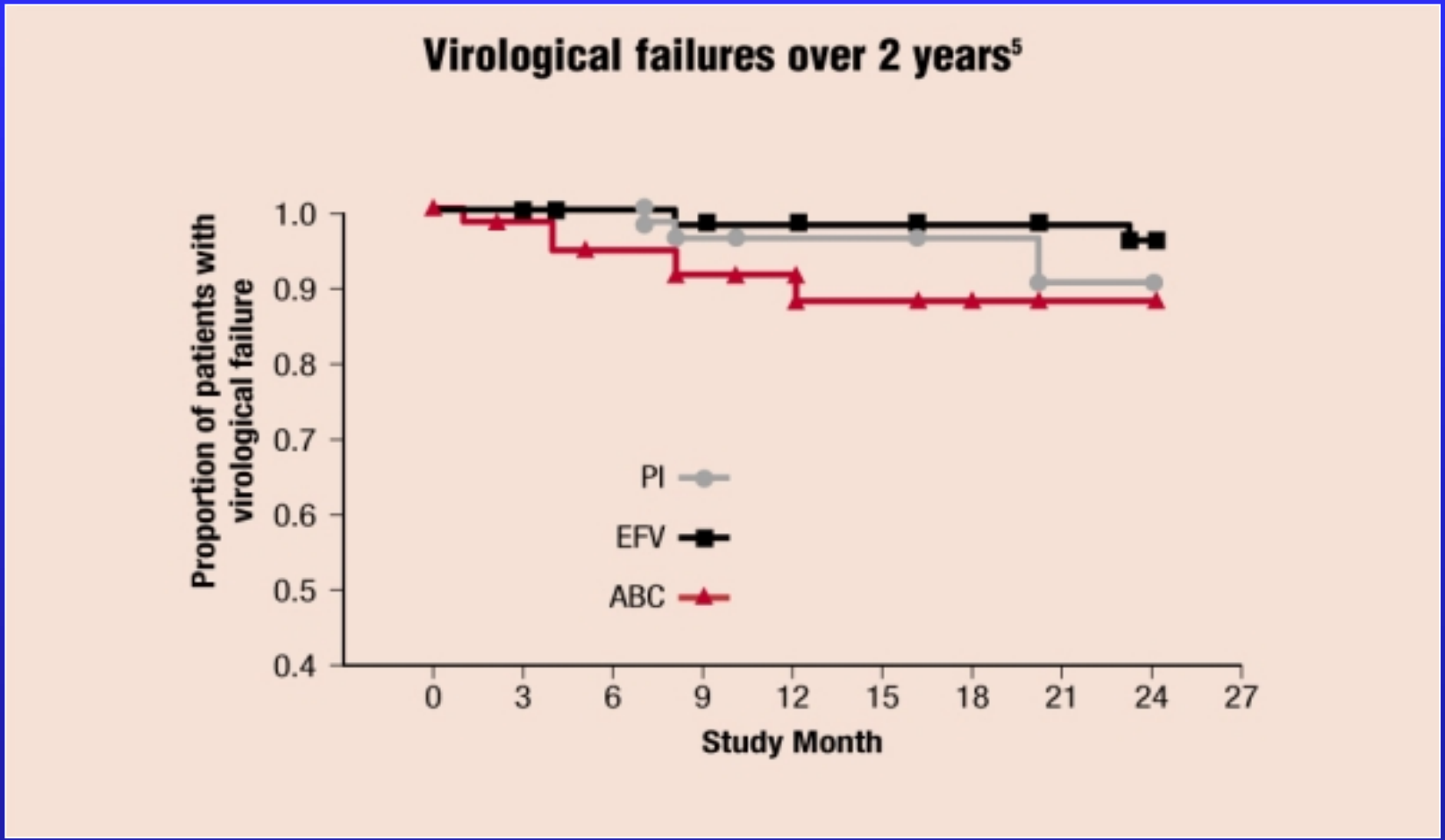
# TRIZAL: Proportion of Subjects with Plasma HIV-1 RNA < 50c/ml at Week 48




Katlama C et al. HIV Medicine 2003;4:79-86

# Switch Maintenance Therapy (Maggiolo)
# Virological Failures over 104 Weeks

**No significant differences across the 3 study arms**




Maggiolo F et al. CID 2003;37:41-49

## Switch studies (PI → ABC), compared to continued PI

| | Virologic failure | |
|---|---|---|
| ***"Optimal" patients*** | **PI arm** | **ABC arm** |
| **Clumeck (CNA30017)** | **1.9% of 103** | **3.8% of 104** |
| **direct start of HAART** | | **2.9%** |
| **Katlama (Trizal)** | **1.0% of 103** | **4. 7% of 106** |
| **direct start of HAART** | | **1.9%** |
| **Maggiolo** | **5.7% of 70** | **10.1% of 69** |
| **direct start of HAART** | | **0%** |
| ***Pre-treated patients*** | | |
| **Opravil (SMT)** | **6.4% of 79** | **15.5% of 84** |
| **direct start of HAART** | | **8.2%** |
| **Martinez** | **n.a.** | **10.7% of 149** |
| **direct start of HAART** | | **2.5%** |

# Switch PI to NRTI or NNRTI: Effect on metabolic complications in randomized trials

| Trial | Switch to | Chol. | Triglyc. | Lipodystrophy |
|---|---|---|---|---|
| Opravil JID 02 | Trizivir | ⇩ | ⇩ | no improvement |
| Clumeck AIDS 01 | ABC | ⇩ | ⇩ | na |
| Katlama: Trizal | Trizivir | ⇩ | ⇩ | improvement |
| Maggiolo CID 03 | ABC | ⇩ | ⇨ | na |
| | EFV | ⇧ | ⇨ | na |
| Ruiz JAIDS 01 | NVP | ⇩ | ⇩ | no improvement |
| Barreiro AIDS 00 | NVP | ⇨ | ⇨ | improvement in 50% |
| Negredo CID 02 | NVP | ⇩ | ⇩ | no improvement |
| | EFV | ⇨ | ⇨ | no improvement |
| DMP266-049 | EFV | ⇨ | ⇨ | no improvement |
| DMP266-027 | EFV | ⇨ | ⇨ | less progression |
| Martinez CROI 01 | EFV | ⇨ | ⇨ | no improvement |
| Martinez NEJM 03 | ABC | ⇩ | ⇨ | no improvement |
| | NVP | ⇨ | ⇨ | no improvement |
| | EFV | ⇨ | ⇨ | no improvement |

# CNA30017: Adherence

- A baseline, une grande proportion de patients affirme prendre toutes les doses des molécules de l'étude ou oublie moins de 1 dose par semaine.

  ABC: 90/101 (89%) ; PI: 77/93 (83%)

- A la semaine 48, cette proportion a augmenté dans le bras ABC et diminué dans le bras IP

  ABC: 86/94 (91%) ; PI: 72/95 (76%)

Clumeck N et al. AIDS 2001;15:1517-26

# Conclusions for simplified therapy with ABC or NNRTI

**Treatment efficacy against HIV infection:**

- documented for patients with ≥6 months of suppressed VL on PI-based HAART
- if treatment started as HAART and no virologic failure: switch to Trizivir (ABC) and NNRTI equally effective
- if NRTI mono/dual therapy prior to HAART:
  switch to NNRTI usually works
  switch to Trizivir (ABC) has high virological failure rate
- no Δ in immunology between PI continuation and simplification
- no Δ in VL in lymphoid tissue shown for both abacavir and efavirenz
- if virologic failure: salvage therapy with PI still works

# Conclusions for simplified therapy with ABC or NNRTI

**Patients' benefit:**

- less treatment changes due to AE / intolerance shown for most switch strategies in comparison to PI continuation
- improved adherence and patient safisfaction shown for all switch strategies
- effect on cholesterol and triglycerides:
  - consistently ↓ only after switch to abacavir
  - variable after switch to nevirapine
  - not significantly lower after switch to efavirenz
- effect on lipodystrophy not finally resolved:
  both fat accumulation and lipoatrophy may reverse, but effects variable between patients and studies

## Who may simplify their HAART to Trizivir?

**Simplification to Trizivir:**

- Well documented regimen, but not for everybody
- Effective in absence of archived NRTI resistance mutations (in pts. who started directly with HAART)
- Spares all other classes for the future
- Best of all simplification strategies for blood lipids
- No CYP interactions

Data not applicable to other triple NRTI regimens

→ individualized assessment in treatment simplification: consider treatment history, cardiovascular risk, and CYP !

→ good adherence always important !

# Triple NRTI regimens that don't work

**Simplification**

Retrospective analysis of 8 pts

- RNA <50 c./ml during median 8 months (7.5 - 18)
- all had started with mainly PI-containing HAART

after switch to ABC + 3TC + TDF:
63% (5/8) failed virologically,
emergence of 184V and 65R mutations

Hoogewerf et al., Lancet 2003;362:1979

⇨ if simplification to ABC:
inclusion of ZDV or d4T seems important

# Triple NRTI regimens that don't work

**Start of therapy in naive patients**

d4T + ddI + ABC [Gerstoft AIDS 03]

d4T + ddI + 3TC [CLASS, ATLANTIC]

TDF + 3TC + ABC [Gallant ICAAC 03, COL40263, TONUS Landman CROI 04]

TDF + 3TC + ddI [Jemsek CROI 04]

- in all of them, higher rates of virological failure than in Trizivir studies
  ⇨ caution if used for simplification
- emergence of 184V and/or 65R mutations

Trizivir [ACTG5095] – differentiate between treatment start and simplification